REMARKS

I. Claim Amendments

By the foregoing amendments to the claims, claims 40, 45 and 46 have been amended to recite that the amount of water added in step (a) is admixed in an amount of between from about 180 wt % to about 190 wt % of the component composition correct formal matters. These amendments are supported at least by claim 2 as originally filed. In addition, claim 2 has been cancelled.

The amendments to the claims, including cancellation of claims, have been made without prejudice or disclaimer to any subject matter recited or canceled herein. Applicants reserve the right to file one or more continuation and/or divisional applications directed to any canceled subject matter. No new matter has been added, and entry of the foregoing amendments to the claims is respectfully requested.

II. Response to Claim Rejections Under 35 U.S.C. § 103

A. Claims 7-10, 14, 18, 20, 24, 26, 28-30, 32, 40-42, 45 and 46 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Speirs (U.S. Patent No. 5,834,021).

B. Claim 2 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Speirs (U.S. Patent No. 5,834,021) and further in view of Enders et al. (EP 0 202 409 A2).

C. Claims 11, 33, 43 and 44 have been rejected under 35 U.SC. § 103(a) as allegedly being unpatentable over Speirs (U.S. Patent No. 5,834,021) and further in view of Mulye (U.S. Publication No. 2004/0224017 A1).

D. Claim 25 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Speirs (U.S. Patent No. 5,834,021) and further in view of Wolozin (U.S. Patent No. 6,472,421 B1).

These rejections are respectfully traversed.

The Examiner has acknowledged that Speirs does <u>not</u> teach producing the specific particle size distribution recited in claim 40. However, it is the Examiner's position that the it would have been customary for an artisan of ordinary skill in the art to determine the optimal parameters of extrusion in order to obtain the desired pellet distribution.

Applicants respectfully note that the Examiner appears to be overlooking the crucial point that the present invention is based on the unexpected observation that particle size distribution can be finely controlled by varying the amount of water used in the process. The Examiner would appear to be approaching the issue of obviousness from the point of view that it was known in the art at the priority date (December 2003) of the present invention that particle size distribution could be controlled by varying the amount of water used in an extrusion/spheronisation process.

Applicants respectfully disagree. None of the prior art cited by the Examiner indicates that the amount of water used in such a process has any impact at all on particle size distribution, let alone the level of fine control which has been observed by the inventors in the present case. Without an appropriate indication in the prior art, a person of ordinary skill in the art would not have been motivated to consider varying the amount of water when trying to control particle size distribution in these pelletization processes.

The prior art does disclose a number of different ways of controlling particle size distribution in extrusion/spheronization processes to make pellets. In this connection, if the prior art cited in the International Search Report is considered, Applicants note that US 2001/0004458 (Opitz *et al*) discloses that particle size distribution may be controlled by varying the diameter of the holes in the perforated disk of the spheronizer. In addition, US 2003/0018000 (Kerrish *et al*) specifies particular conditions (i.e. jacket water temperature, groove plate configuration, maumerizer speed setting, and spheronizing time) for spheronizing the extrudate to produce pellets. Further, the Speirs reference specifies particular conditions (i.e. extrusion tube diameter, extrusion rate, spheronizer plate size and plate rotation rate, and spheronizing time) for spheronizing the extrudate to produce pellets. Since these factors were all known at the priority date to potentially play a part in controlling particle size distribution, Applicants acknowledge that the skilled person would have considered these factors when faced with the problem of optimising particle size distribution. However, none of these references teaches or even suggests that water may have such a significant role to play. In fact, the Kerrish *et al* reference even indicates that wetting agents other than water (e.g. polyethylene glycol) could be used, which suggests that the use of water may not even be an essential feature of the pelletization process.

In view of the fact that it was known to control particle size distribution by focussing on these other factors, it is Applicants' view that the Examiner improperly relying on hindsight analysis when concluding that the skilled person would inevitably have considered controlling the amount of water to control particle size distribution, particularly when there is nothing in the prior art to suggest doing so.

Nevertheless, to advance prosecution but not to acquiesce to the rejections, Applicants have amended the claims to require that the amount of water used in the process is admixed to an amount of from about 180 wt % to about 190 wt % of the component composition. This amendment emphasizes the importance of controlling the amount of water in order to achieve the desired particle size distribution. However, Applicants would like to point out that, by amending the claims in this way, Applicants are not conceding that the broader concept of using water to finely control particle size distribution is known or obvious over the prior art.

The Examiner has suggested that the embodiment recited in the claims as amended is obvious over the Speirs reference in view of Enders *et al*). Applicants respectfully disagree with the Examiner for at least the following reasons.

As discussed above, Speirs does not teach or suggest that the particle size distribution of the pellets produced in the reference process may be controlled to any extent, let alone to the unexpectedly focused extent observed by the present inventors, simply by varying the amount of water used. In addition, the Speirs reference does not teach or suggest the use of any particular amount of water in the process, let alone the use of not only such a narrow range of water (about 180 wt % to about 190 wt %), but also such a large amount of water overall. It is even more surprising that such a small variation in the amount of water used should have such a significant impact on size distribution when the large amount of water is considered.

The first point to make regarding Ender *et al* is that it relates to a different field of technology to the present invention and the subject matter disclosed in Speirs. In this connection, both the present invention and the subject matter disclosed in Speirs concern processes for producing a *pharmaceutical* products. Indeed, the present invention is an improvement of the process disclosed in Speirs. In contrast, Ender *et al* is concerned with a process for producing microorganisms for *food and agricultural purposes*. These technological fields are not the same as evidenced by the fact that Enders *et al* has been classified using

entirely different International Patent Classification (IPC) numbers. In this connection, the primary IPC for both the present invention and Speirs is given as A61K 9/16, i.e. medical preparations characterized by a special physical form. However, in contrast, the primary IPC for Enders *et al* is given as C12N 11/04, i.e. carrier bound immobilized enzymes. Ender *et al* has also been placed in A21D (baking) and A21K (food) but neither of these classes relate to pharmaceutical products or processes. On this basis, Applicants submit that the skilled person, when presented with the problem of improving the Speirs process for producing pharmaceutical pellets, would not have turned to Enders *et al* since it relates to a different technical field.

Enders *et al* discloses a microencapsulation process for microorganisms. The process involves mixing culture concentrates of lactic acid-producing bacteria with a bulking agent and sufficient water to form a homogenous wet granulation having a water content of about 35 to 65 wt %, and preferably 38 to 45 wt %. The granulation is then extruded and spheronized to produce pellets, and after spheronization the pellets are dried. In the exemplified embodiments, the wet granulations contain about 37 wt % water.

The Examiner notes that the range of 180 wt % to 190 wt % water based on the dry weight of the component composition in the present invention, equates to 64.3 wt % to 65.5 wt % water based on the total weight of the wet composition. The Examiner then concludes that, since Enders *et al* discloses a range of water than overlaps with the claimed range, the present invention as defined by the claimed range is *prima facie* obvious over Speirs and Enders *et al*. However, the Examiner has overlooked the unexpected effect observed by the present inventors.

The inventors have demonstrated in the Examples that even a small amount of water outside the claimed range has a significant impact on the particle size distribution. In this connection, the inventors have demonstrated (see Example 4) that using 182.5 wt % water provides a yield of 96.5 % of pellets having the required diameter; that the yield drops substantially to 91% using 180 wt % water (see Example 2); and that the yield drops substantially again to 85 % using 177.5 wt % water (see Example 5).

These results indicate that reducing the amount of water by as little as 5 wt % from 182.5 wt % (i.e. ~2.7% of the total amount of water) reduces the overall yield of particles having the required diameter by over 11%. It is reasonable to assume that a further reduction in the amount

of water used to, say, 175 wt %, would mean that particle size distribution would fall outside the range claimed. This result is significant and entirely unexpected.

Enders *et al* clearly did not envisage such a result since this reference suggests using 35 to 65 wt % water based on the total weight of the wet composition, which equates to 53.8 wt % to 185.7 wt % water based on the dry composition. In other words, Enders *et al* suggest using a large range of amounts of water, e.g. up to 175 wt %, that are too small to produce pellets having the required size distribution.

It should be noted in this regard that the upper limit of the preferred range of water in Enders *et al* is 45 wt % based on the wet granulation, which equates to 81.8 wt % based on the dry composition. In addition, Enders *et al* exemplifies using 37 wt % based on the wet granulation, which equates to 58.7 wt % based on the dry composition. In other words, the actual overlap between the range of the present invention and the range disclosed in Enders *et al* is very small. In addition, the overlap is at the end of the range of Enders *et al* that is entirely speculative and not exemplified, and far removed from the actual range practiced by Enders *et al*. Clearly, Enders *et al* is primarily concerned with producing pellets using amounts of water that are far outside the range claimed in the present application.

Finally, the additional references cited by the Examiner (i.e. Mulye and Wolozin) do not remedy the serious deficiencies of Speirs and Enders *et al*.

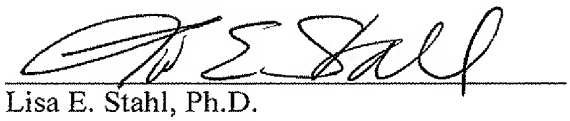
In view of the above, the references cited by the Examiner, taken alone or in the cited combinations, do not teach or suggest the subject matter of the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions related to this response, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney at the below-listed telephone number concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

By: 
Lisa E. Stahl, Ph.D.
Registration No. 56,704

BACON & THOMAS PLLC
625 Slaters Lane, Fourth Floor
Alexandria, Virginia 22314-1176
703.683.0500

Date: September 16, 2010